REMARKS

Claims 8-22 are pending in this application. Claims 8-12 have been amended to be directed towards high risk HPV. Claims 13-22 have been added; however, no new matter has been introduced by the addition of these claims. These claims are simply a subset of the original pending claims. Claims have been amended and added in order to expedite prosecution of the instant application and to eliminate issues from the present application. Applicants respectfully request entry of these claims.

Information Disclosure Statement

Enclosed herewith is an English translation of the German patent DE 44457969.3. Please consider the IDS and reference listed in the Form 1449, including this German patent. (Exhibit A), enclosed herewith.

Specification Rejections

The Examiner objects to the specification for the introduction of new matter as a result of the June 13, 2003 amendments. The Examiner specifically points to the phrase "isolated and" at page 23, line 14 of the instant application. In order to expedite prosecution of the instant application, applicants have amended the specification to delete the phrase "isolated and."

Regarding the Examiner's objection to the insertion of the phrase "to calibrators and cellular RNA," at line 20, applicants respectfully direct the Examiner's attention to Examples 1-4. Specifically at page 22, lns. 1-3, and at page 23, lns. 15-21, where RNA calibrators and cellular RNA are added to the probe mix.

For the foregoing reasons, applicants respectfully request reconsideration and withdrawal of these objections.

Declaration Under 37 C.F.R. §1.132 Objections

Applicants have amended the Declaration to address the Examiner's concerns. Enclosed herewith is a revised executed Declaration which now reads "that all statements

made herein of my own knowledge are true and that all statements made on information and belief are believed to be true" as executed by the declarant, Dr. Attila T. Lorincz (Exhibit B). Applicants respectfully request that the objections to the Declaration under 37 C.F.R. §1.132 be reconsidered and withdrawn in view of the previous described amendments.

With respect to the Examiner's contention that HPV 18 and HPV 31 "are not representative of the entire genus" (Advisory Action dated February 7, 2005), applicants assert that high risk HPV types are limited to a group including HPV 16, 18, 31, 33, 35, 39, and 41-45 (Declaration, pg. 5-6; Koromilas, et al.; Exhibit 13; pg. 158, Col. 1, ¶2). High risk HPV types have been characterized in the Declaration attached hereto. Support for the limited characterization of HPV high risk types may be found in the literature, including zur Hausen (Exhibit 2) which provides Table 1 which characterizes HPV types 1-70; Koromilas, et al. (Exhibit 13) which reports of high risk HPV types 16, 18, 31, 33, 35, 39, and 41-45; Stoler, et al. (Exhibit 5) which demonstrates that 80% of invasive cervical cancers may be attributed to infection by HPV types 16, 18, 31, and 45; Stoler (Exhibit 16) further describes varying risk types including high risk HPV types; and Chow and Broker (Exhibit G) which provides an overview of HPV types, disease manifestations and oncogenic risk, and further support for high risk HPV types are commonly known in the art.

Applicants have amended the claims to refer to high risk HPV types. Those skilled in the art understand that high risk HPV types are limited to a subgroup of HPV types, including HPV 16, 18, 31, and 33. For these reasons, applicants believe that the claims as amended with high risk HPV types are in condition for allowance. Reconsideration and withdrawal of these rejections are respectfully requested.

35 U.S.C. §112 Rejections

Claims 8-12 stand rejected under 35 U.S.C. §112, first paragraph for non-enablement because allegedly, from the specification, "it is not known what HPV16 mRNA ratios exist in HaCaT cells for transcript combinations other than (E6+E7)/L1." The Examiner contends that "while the instant claims are directed to methods of, *e.g.*, detecting or predicting cancer, cancer risk, or neoplastic onset in a patient, the specification does not provide any evidence that the HPV gene transcript ratios set forth in the claims are associated with transformation,

cancer, disease stage, etc., in a patient." Furthermore, the Examiner contends that "neither the specification nor the teachings of the prior art establish a correspondence or correlation between the particular ratios of HPV transcripts recited in the instant claims and "HPV-induced cell transformation" or risk for/ onset of/stage of HPV-induced cancer in a patient. Applicants respectfully disagree with this rejection.

Applicants assert that (1) the cell line models described in the specification correlate to stages of HPV-induced disease in patients; (2) there is a strong correlation between HPV infection and cancer; and (3) the claimed diagnostic assays are useful in the diagnosis of these HPV-induced diseases in patients. Applicants further assert that the claims are fully enabled as the disclosure teaches how to make and use the assays for screening and diagnosis purposes in patients.

Details concerning the cell line model systems and their correlation to disease states in patients are provided in the instant specification.

> HaCaT cells were infected with HPV 16 by the procedure of White et. al. (White (1998)) to produce an episomal (non-integrated, total sequence, not spliced) HPV infection. Approximately 1 copy of HPV16 was present for every 40 cells. These cells are considered a representative of early stage infection or CIN I (cervical intraepithelial neoplasia). W12 cells contain approximately 100 copies of episomal HPV16 DNA and represent pre-malignant, immortalized cells or CIN II or CIN III. SiHa cells contain 1-2 copies of HPV16 integrated into the genome. These cells are considered to represent cancer.

See page 23, first paragraph, emphasis added. In addition, applicants include herewith two articles that describe the use of these same cell lines as models for human cancer. The first article (Diem, C. and Runger, T. M. (1997) "Processing of three different types of DNA damage in cell lines of a cutaneous squamous cell carcinoma progression model," *Carcinogenesis* 18:657-662) describes a model that "comprised the spontaneously immortalized non-tumorigenic human keratinocyte cell line HaCaT." *See* Abstract. The second article (Coleman, N. and Stanley, M. A. (1994) "Expression of the myelomonocytic antigens CD36 and L1 by keratinocytes in squamous intraepithelial lesions of the cervix," *Hum. Pathol.* 25:73-79) describes the cervical keratinocyte cell line W12 as a model for low-grade squamous intraepithelial lesions and the SiHa cell line as a model for high-grade

squamous intraepithelial lesions. *See* Abstract. Therefore, these publications provide evidence such that the skilled artisan would recognize the cell lines used in the instant specification as correlated with specific stages of cell transformation events in patients.

The specification also provides teachings that there is a strong correlation between HPV infection and human disease. "Individual types of human papillomaviruses (HPV) which infect mucosal surfaces have been implicated as the causative agents for carcinomas of the cervix, anus, penis, larynx and the buccal cavity, occasional periungal carcinomas, as well as benign anogenital warts." *See* page 3, lines 13-16. Further, applicants provide two publications which describe a strong link between HPV infection and human disease, (1) zur Hausen, H., (1996) entitled "Papillomavirus infection a major cause of human cancers," published in *Biochimica et Biophysica Acta* (1288:F55-F78) (Exhibit 2); and (2) zur Hausen (1989) entitled "Papillomaviruses as Carcinomaviruses," published in *Advances in Viral Oncology*, (Vol. 8, G. Klein, ed., Raven Press, New York, pp. 1-26) (Exhibit C).

The model system examples described in the specification constitute working examples because the examples correlate with the claimed methods of assessing HPV-induced disease in patients. "An in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention." MPEP: 2164.02. "In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Id. A rigorous or an invariable exact correlation is not required. As stated in *Cross v. Iizuka,* 753 F.2d 1040, 1050 (Fed Cir. 1985) (Exhibit D):

> [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonably based upon the probative evidence. (Citations omitted.)

Applicants emphasize that they are not required to show their claimed methods in patient samples. The Federal Circuit has repeatedly held that establishing therapeutic efficacy in

humans is the job of the FDA, not the PTO. *See In re Branna*, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995) (Exhibit E); *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) (Exhibit F). The Federal Circuit has recognized that pharmaceutical inventions necessarily include the expectation of further research and development, and such inventions become useful well before they are ready to be administered to humans. *See In re Branna*, 34 USPQ2d at 1442. Accordingly, to require proof of efficacy in humans

> ...would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through cancer research and development, potential cures in many crucial areas such as the treatment of cancer. *In re Branna*, 34 USPQ2d at 1443.

Therefore, the Examiner has set a higher standard for applicants than is required by law. Applicants are required only to show that there is a "reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity" *Cross v. Iizuka*, 224 USPQ 739, 747 (Fed. Cir. 1985) (Exhibit D); see MPEP §2164.02. Moreover, *in vivo* activity can include activity in humans and/or activity in a standard animal model. The Federal Circuit has held:

> [I]t is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans. *In re Branna*, 34 USPQ2d at 1442.

Applicants note that the Examples of the instant application teach the use of HPV mRNA ratios for assessing disease stage *in vitro*. In the Declaration submitted herewith under 37 C.F.R. §1.132, Dr. Lorincz states that "The teaching of the application can be used by the skilled practitioner for assessment and diagnosis of disease stage in cells, including patient cells." (paragraph 5). Dr. Lorincz further states that "For the experiments described, *in vitro* results are generally correlative with *in vivo* results. Moreover, *in vitro* data are

routinely used by those in the art who apply and extrapolate the findings and outcomes of *in vitro* cell culture experiments to *in vivo* use." (paragraph 5).

According to Table 2 of the instant specification, the W12 cell line is representative of the pre-malignant stage of HPV-induced cervical disease. It is also considered to have a borderline cell status that includes early-stage infection and pre-malignant cells correlating to HPV-infected HaCaT and W12 cells, respectively. In these borderline cases, variations in the mRNA ratios may be expected. It is important to look at the mRNA ratio profile in order to assess risk of HPV-induced disease. Therefore, the three cell lines are predictive of results that would be obtained in assaying patient samples.

In addition to the previous arguments that the HPV-infected HaCaT, SiHa, CaSki, HeLa and W12 are universally recognized model systems of human epithelium in a patient at various stages of cancer progression, applicants respectfully direct the Examiner's attention to the Declaration at pages 2-6, paragraphs 6-26 for further support.

As evidenced by the correlation between the cultured cell model systems and human disease, the HPV gene transcript ratios also apply to different types of HPVs and cancers. Applicants respectfully direct the Examiner's attention to the Declaration at pages 7-11, paragraphs 28-38, which supports the methods using other types of HPVs, specifically, HPV 18 and HPV 31. No undue experimentation would be required for one skilled in the art to diagnosis and/or monitor cancer in a patient using the methods of determining the HPV gene transcript ratios as described and claimed in the instant application. For example, the HPV gene transcript ratio of (E6+E7)/L1 for HPV16, HPV18, and HPV31 are greater than 2 in neoplastic cell lines.

The specification teaches how to make and use the assays for diagnosis purposes thereby fully enabling the claims. The specification describes "sources of cell samples for assessing HPV-based disease include cervix, vagina, vulva, anus, penis, larynx, buccal cavity, lymph nodes, malignant deposits in any part of the human body, and epidermis; all of which are known sites of HPV infection and pathology." See page 18, lines 5-8. "Examples of disease states for assessment using the present invention include, but are not limited to neoplasms and cancer. Disease states of interest are HPV-based disease -- including HPV infection, cervical intraepithelial neoplasia (CIN), and cancer, atypical

squamous cells of undetermined significance (ASCUS), warts, condylomata, epidermo dysphasia verruciformis and other skin diseases, laryngeal papilloma , oral papilloma and conjucitival papilloma." See page 7, lines 14-19. Once the sample is obtained from the patient, the specification describes that the "[e]xpression of genes of interest, such as the HPV E6, E7, L1, E4, and E2 genes, can be assessed using any suitable method." See paragraph spanning pages 12 and 13. Further, the specification teaches specific useful techniques for measuring the level of expression of a gene of interest in a cell sample. See page 13, lines 14-21. Thus, the specification provides sufficient guidance to the skilled artisan on how to make and use the claimed diagnostic assays for screening purposes in patients. In view of the arguments presented above, applicants respectfully request reconsideration and withdrawal of the 37 C.F.R. §112, first paragraph rejection.

With respect to the Examiner's contention that neither the specification nor teachings of the prior art establish a correspondence or correlation between the particular ratios of HPV transcripts recited in the instant claims and "HPV-induced cell transformation" or risk for/ onset of/ stage of HPV-induced cancer in a patient, applicants respectfully disagree and direct the Examiner's attention to Table 2, which indicates that an episomal early stage HPV infected model system has an HPV gene transcript ratio of about 0.7, or less than 2; and a pre-malignant cell line and a malignant cell line have HPV gene transcript ratios of greater than 2. HPV16 gene transcript ratios for the HaCaT model system of human early stage infection other than the combination of (E6+E7)/L1 mRNA ratios are not expected to exceed a ratio of 2 since this is the threshold for cell transformation.

The Examiner contends that ratios of HPV16 gene transcripts other than (E6+E7)/ L1 were not presented for HaCaT cells (Table 2) and it is not known what HPV16 mRNA ratios exist in HaCaT cells for transcript combinations other than E6+E7/ L1. Although the Examiner contends that it is not known whether other HPV gene transcript combinations other than (E6+E7)/L1 exist in HaCaT cells, applicants respectfully point out that the data for the HaCaT cells indicated by "ND" were expected to be below 2, which correlates to the early-stage infection of HPV-induced disease. In fact, when the HPV gene transcript ratio has a denominator greater than the numerator, the ratio will be small. With respect to the HaCaT data of Table 2, the denominator is greater than the numerator and

accordingly have an HPV gene transcript ratio of less than 1. Since the ratios would be expected to be less than 2, one skilled in the art would understand that these HPV gene transcript ratios do not suggest high risk disease, and fall into the early stage infection category. Table 2 further shows that an HPV gene transcript ratio of greater than 2 correlates to malignant cells of HPV-induced disease, *i.e.*, SiHa cells.

Furthermore, the Examiner contends that it is unpredictable based on Stoler, et al. and the specification as to whether detection of such ratios in patients would be useful in diagnosis of disease caused by other HPV types. However, applicants present herewith a Declaration which addresses the use of the HPV mRNA ratios of other HPV types, including HPV 18 and HPV31, to diagnose the HPV-associated disease states.

The Examiner contends that one skilled in the art would not be able to practice the claimed invention since the other combinations of HPV mRNA ratios are not presented. Applicants remind the Examiner that as defined in MPEP 2163, a "representative number of species" are species which are representative of the entire genus. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each and every species that the genus embraces. In fact, a satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicants were in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed.

Applicants have amended the claims to be directed to high risk HPV, which is supported throughout the instant specification, and more specifically, at page 1, lns. 24-25 and at page 8, first paragraph. The high risk HPV types have been characterized and are commonly known in the art. For example, Mark Stoler ("Human Papillomaviruses and Cervical Neoplasia: A Model for Carcinogenesis" *Int. J. Gynecol. Pathol.*, 19:16-28, 2000; Exhibit 5); describes the varying risk types of HPV at page 18, left column, which include high risk HPV 16, 18, 31, 33. Stoler further associates active transcription of HPV DNA with cervical neoplasia and the expression of the E6 and/or E7 region (page 20, left col., first full paragraph).

The Examiner's attention is respectfully directed to Chapter 12, pages 279-280 of "Small DNA Tumor Viruses" by Louise Chow and Thomas Broker (*Viral Pathogenesis*, edited by Neal Nathanson, et al. Lippincott-Raven Publishers, Philadelphia © 1997; Exhibit G) which discusses the high risk HPVs and the genes associated with them. In particular, E6, E7 gene expression is increased in high-grade lesions and carcinomas, while E1, E2, E4, and E5 is low. Also discussed is the absence of L1 and L2 signals from high-grade lesions. One skilled in the art would understand from reading the instant specification and the Chow and Broker publication, the expression of these genes correlates to the natural tendencies and biology of all high-risk HPV types, including HPV types 16, 18, 31, and 33. Accordingly, the skilled artisan would understand that there is a correlation between the HPV types and HPV-induced neoplasia and how to determine the risk of HPV-induced neoplasia from the claimed HPV mRNA ratios.

Therefore, applicants respectfully submit that the originally filed specification of the application enables any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims of the application. Because 1) applicants are not required to prove efficacy of the claimed methods in humans; 2) applicants are required only to show a reasonable correlation of the disclosed *in vitro* results and an *in vivo* activity; 3) *in vivo* activity can be evidenced by activity in humans and/or activity in a model system; 4) the Declaration of Dr. Lorincz evidences that *in vitro* results are generally correlative with *in vivo* results for the experiments of the instant application; and 5) applicants have pointed to the art which demonstrates that high risk HPV types are limited to a group including HPV 16, 18, 31, 33, 35, 39, and 41-45, applicants believe that the application has met the requirements for enablement under 35 U.S.C. §112, first paragraph.

Double Patenting Rejection

Claims 8-12 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-5, respectively, of U.S. Patent No. 6,355,424 B1. Applicants enclose herewith a terminal disclaimer (Exhibit H), which through the Attorney of Record, disclaims the terminal part of the statutory term of any patent granted on the instant

application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §§§§154 to 156 and 173, of United States Patent No. 6,355,424. The filing of a terminal disclaimer to obviate a rejection based on non-statutory double patenting is not an admission of the propriety of the rejection. *Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870 (Fed. Cir. 1991) MPEP 804.2.

Applicants acknowledge that the Examiner has found that the terminal disclaimer filed October 18, 2004 has overcome the Double patenting rejection. Enclosed herewith is a copy of the previously filed terminal disclaimer (Exhibit H).

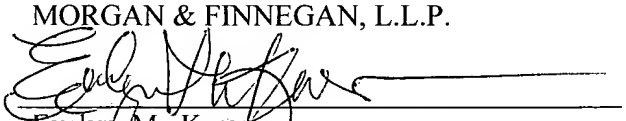
CONCLUSION

Based on the foregoing amendments and remarks, applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for the timely consideration of this amendment under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account No. 13-4500, Order No. 2629-4005US4.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.



Dated: May 18, 2005 By: Evelyn M. Kwon
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